

REMARKS

Claims 80-81 have been amended. Claims 33 and 56 have been canceled. Claims 1-26, 35-53 and 60-79 were previously canceled. Claims 27-34, 54-59 and 80-82 are currently pending in this application.

35 U.S.C. § 102(b)

Claim 1 stands rejected under 35 U.S.C. § 102(b) as being anticipated by the Physicians' Desk Reference 1995 (PDR). Specifically, the Office Action states that the PDR discloses a diazepam solution. As claim 1 is not pending and no pending claims specifically recite diazepam, Applicant assumes that this rejection was made in error.

35 U.S.C. § 103(a)

Claims 27-34, 54-59 and 80-82 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Déihl (WO 9413280) in view of Fassberg et al. (EP 0656206) in further view of Kanios et al. (U.S. Patent No. 5,719,197) or alternatively the Physicians' Desk Reference 1995 (PDR). This rejection is respectfully traversed.

Independent claims 80, 81 and 82 recite methods for administering an effective amount of a pharmacologically active compound to a mammal to provide transmucosal absorption of a pharmacologically effective amount of the active compound through the oral mucosa of the mammal to the systemic circulatory system of the mammal. Independent claim 80 recites "spraying the oral mucosa of the mammal with a propellant free buccal spray composition, containing . . . an active compound . . . selected from the group consisting of clozapine, phenytoin or a pharmaceutically acceptable salt thereof; and a polar solvent." Independent claim 81 recites "spraying the oral mucosa of the mammal with a propellant free buccal spray composition, containing . . . an active compound . . . selected from the group consisting

of clozapine, phenytoin or a pharmaceutically acceptable salt thereof; and a non-polar solvent." Independent claim 82 recites spraying the oral mucosa of the mammal with a propellant free buccal spray composition, containing . . . an active compound . . . comprising a benzodiazepine; and a non-polar solvent."

The Office Action asserts that Deihl provides "general teachings of formulations for buccal mucosal administration" (Office Action at 6). The Office Action acknowledges, as it must, that Deihl fails to disclose the active compounds recited by the present claims, and also fails to disclose the use of the presently claimed solvents or amounts, including polyethylene glycol or non-polar solvents.

Based on the alleged "general teachings" of Deihl, the Office Action asserts that it would have been obvious to "have looked in the art for other specific solvents suitable for spray formulations of liquid carriers, as taught by Fassberg et al., with reasonable expectations of successfully preparing suitable formulations for various therapies." (Office Action at 6). Because Fassberg et al. also fails to disclose or suggest various actives and components recited by the present claims, the Office Action relies on Kanios et al. or the PDR, and asserts that "it is obvious to one of ordinary skill in the art to have substituted any suitable active agent for the analgesics of Deihl's buccal spray formulations as...taught by Kanios et al. or the Physicians' Desk Reference." (Office Action at 6, emphasis added).

Thus, the Office Action is premised on the PTO's reading of Deihl as a general teaching from which one may allegedly extrapolate to multiple other solvents and amounts, and to other pharmaceutically active agents, and do so with a reasonable expectation of success. Remarkably, this reasoning is based on Fassberg et al., which is not directed to buccal sprays, much less to propellant-free sprays as claimed, and on Kanios et al. and the PDR, which are not directed to buccal sprays at all. Aside from

the shortcomings of these secondary references, Deihl itself is far from a general teaching of buccal sprays from which one of ordinary skill at the time of the present invention would have expected much of anything at all, much less that one of ordinary skill would have been motivated to modify Deihl to achieve the presently claimed methods for administering clozapine, phenytoin or a benzodiazepine.

More specifically, at the time of the present invention, Deihl would not have been considered a credible or relevant teaching and, for the reasons discussed below, would not have been relied upon in any capacity by those skilled in the art at the time that the present invention was made. Deihl purports to teach a sprayable, therapeutic, acetaminophen or ibuprofen composition, where acetaminophen or ibuprofen is capable of being absorbed into the bloodstream through the buccal mucosa. Deihl's composition includes ibuprofen or acetaminophen and aqueous ethanol. Deihl states that for treatment of a headache, a patient sprays four measured sprays into the mouth. Each spray is 50 microliters and contains 1 milligram of acetaminophen or ibuprofen. This treatment may be repeated once after five minutes. That is, Deihl teaches a total dose of 4-8 milligrams of acetaminophen or ibuprofen. Deihl at 5.

Even assuming 100 percent bioavailability, those of ordinary skill in the art would readily appreciate that a 4-8 milligram dose of acetaminophen or ibuprofen is not even remotely therapeutically effective. According to GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 10th ed., the oral dosage for acetaminophen is 320 to 1000 milligrams for adults and 40 to 480 milligrams for children with about 88% bioavailability. For ibuprofen the oral dosage for adults is 400 milligrams for mild pain to as much as 3200 milligrams for arthritis, with about 80% bioavailability. Thus, even assuming 100% bioavailability, a patient receiving Deihl's formulation would receive only 4-8 milligrams of active agent, a tiny fraction of what is required for any

therapeutic effect. A patient would need to administer a completely unworkable number of spray activations of Deihl's formulation to realize any potential therapeutic effect, but by that point the volume of fluid sprayed would be so great as to result in swallowing and thus avoid mucosal absorption. Therefore, one of ordinary skill in the art would have readily appreciated that Deihl's buccal spray composition and method is unworkable and ineffective.

One of ordinary skill in the art would also have appreciated that Deihl's ineffective, unworkable spray teachings were quite consistent with the state of the art at the time the present invention was made. Those skilled in the art generally perceived buccal administration as an ineffective and unworkable delivery method. For example, REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 19th ed. (1995) at 710, a copy of which is enclosed, states that "when only small amounts of drugs are required to gain access to the blood, the buccal route may be satisfactory, providing the physicochemical prerequisites for absorption by this route are present in the drug and dosage form. Only a few drugs may be given successfully by this route." (emphasis added)

This well accepted view of buccal administration was based in part on the belief that the relatively rapid clearing of the mouth by swallowing limited the buccal absorption phase to between about 5-10 minutes. Therefore, it was understood that the amount of drug delivered would be very small causing the blood plasma levels of drugs administered buccally to rise slowly. Thus, buccal administration was generally disfavored and thought to be an ineffective and unworkable delivery method. Consequently, the disclosure of Deihl itself, as well as the general understanding in the art, were completely inconsistent with the Office Action's assertions and reasoning that Deihl provides a general teaching from which one of ordinary skill would have been motivated to extrapolate to diverse pharmaceutical actives and solvents, much less to

do so with any expectation of success in administering clozapine, phenytoin or a benzodiazepine via a buccal spray.

In addition, Fassberg et al. relates to an inhalation aerosol, which is a propellant-containing spray or powder formulation for oral and/or nasal administration. Fassberg et al. does not disclose or suggest any propellant-free method for the delivery of an active agent by spraying the buccal mucosa of a mammal. Fassberg et al. clearly does not teach or suggest that buccal administration of any actives is generally effective.

According to the PTO, it would have been obvious to modify Diehl with the solvents disclosed by Fassberg et al. (Office Action at 4.) To the contrary, one of ordinary skill would not have used the Fassberg et al. solvents to modify the formulations of Diehl, because Fassberg et al. explains that the solvents used in its inhalation formulations are only present to facilitate the propellant. Diehl has no propellant and the present claims exclude propellants. Accordingly, one of ordinary skill in the art would not have been motivated to modify Diehl with the teachings of Fassberg et al., for this additional reason.

Likewise, one of ordinary skill in the art would not have been motivated to modify Diehl with the teachings of Kanios et al. to achieve the compositions and methods recited by the presently pending claims. Kanios et al. refers to an intermediate composition that is made into a "finished dosage form" by applying a flexible backing which further defines the size and shape of the finished dosage form, which is, among other things, occlusive to water permeation in vivo. Kanios et al. is entirely unrelated to a buccal spray method for transmucosal administration.

Similarly, one of ordinary skill in the art would not have been motivated to modify Diehl with the PDR to achieve the methods recited by the presently amended claims. The PDR is cited for teaching a diazepam solution, and is unrelated to any buccal spray method for transmucosal administration.

For at least these reasons, Applicant respectfully requests that this § 103 rejection be withdrawn.

Claims 27-34, 54-59 and 80-82 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Fu et al. (WO 9303751) in view of the PDR. This rejection is respectfully traversed.

Like Deihl, the Office Action uses Fu et al. as a general teaching from which one of ordinary skill could have allegedly extrapolated to any other pharmaceutical active, and have done so with an expectation of success, based on "the general teachings of formulations for buccal mucosal administration of Fu et al." (Office action at 7). Again, the Office Action is mistaken, as Fu et al. is anything but a general teaching that would have motivated one of ordinary skill to look to the PDR with any expectation of success, and the general state of the art at the time of the present invention was to the contrary (as discussed above, citing Remington).

Fu et al. refer to compositions for the sublingual delivery of specific polypeptides that are normally degraded upon oral administration. Fu et al. is directed to the administration of polypeptides that can not be ingested. These polypeptides are very limited in scope. Fu et al. only present examples of formulations containing leuprolide acetate and deslorelin acetate, which is closely related to leuprolide acetate. At most, Fu et al. establish that buccal administration can be used for specific polypeptides and only when a permeation enhancer is employed. See e.g., Fu et al. at

10-12 (showing low bioavailability for exemplary formulations, less than 25% bioavailability for all but one formulation). This underscores the general state of the art regarding the problem with buccal delivery as described by Remington.

The examples provided by Fu et al. are limited to two closely related polypeptides that can not be administered by oral ingestion. Thus, Fu et al. would not have been viewed as a general teaching for successful buccal administration of a variety of pharmaceutical actives. Therefore, one of ordinary skill in the art would not have been motivated to modify Fu et al. with any of the pharmaceutical actives of the PDR, as stated in the Office Action. For at least these reasons, Applicant respectfully requests that this rejection be withdrawn.

Double Patenting

Claims 27-34, 54-59 and 80-82 are provisionally rejected over claims of several co-pending applications. As the claims of the present application, as well as those of the co-pending applications are subject to change, Applicant respectfully requests that the provisional rejections be held in abeyance until such time as this or a co-pending application is in a condition for allowance.

In view of the above, Applicant believes the pending application is in condition for allowance. If the Examiner should believe that anything further may be required to place this application in even better form for allowance, she is cordially invited to telephone the Applicant's undersigned representative.

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Respectfully submitted,

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Table 1—Rates of Entry of Drugs in CSF and the Degrees of Ionization of Drugs at pH 7.4^a

Drug/chemical	% binding to plasma protein	pK _a ^b	% un-ionized at pH 7.4	Permeability constant (P min ⁻¹) ± S.E.
<i>Drugs mainly ionized at pH 7.4</i>				
5-Sulfosalicylic acid	22	(strong)	0	<0.0001
N-Methylnicotinamide	<10	(strong)	0	0.0005 ± 0.00005
5-Nitrosalicylic acid	42	3.3	0.001	0.001 ± 0.0001
Salicylic acid	40	3.0	0.004	0.008 ± 0.0004
Mecamylamine	20	11.2	0.018	0.031 ± 0.0016
Quinine	76	8.4	0.09	0.073 ± 0.0061
<i>Drugs mainly un-ionized at pH 7.4</i>				
Barbital	<2	7.5	55.7	0.028 ± 0.0028
Thiopental	76	7.8	61.3	0.50 ± 0.051
Pentobarbital	40	8.1	33.4	0.17 ± 0.014
Aminopyrine	20	5.0	99.6	0.25 ± 0.020
Aniline	15	4.6	99.8	0.40 ± 0.042
Sulfaguanidine	6	> 10.0 ^b	> 99.8	0.008 ± 0.0003
Antipyrine	8	1.4	> 99.9	0.12 ± 0.013
N-Acetyl-4-aminopentipyrine	<3	0.5	> 99.9	0.012 ± 0.0010

^a The dissociation constant of both acids and bases is expressed as the pK_a, the negative logarithm of the acidic dissociation constant.

^b Sulfaguanidine has a very weakly acidic group (pK_a > 10) and two very weakly basic groups (pK_a 2.75 and 0.5). Consequently, the compound is almost completely undissociated at pH 7.4.

for all practical purposes, only the un-ionized form is said to pass through the membrane. This has become known as the principle of *nonionic diffusion*.

This principle is the reason that only the concentrations of the un-ionized form of the barbiturates are plotted in Fig 9.

For the purpose of further illustrating the principle, Table 1 is provided.⁷ In the table, the permeability constants for penetration into the cerebral spinal fluid of rats are higher for un-ionized drugs than for ionized ones. The apparent exceptions—barbital, sulfaguanidine and acetylaminoantipyrine—

may be explained by the dipolarity of the un-ionized molecules. With barbital, the two lipophilic ethyl groups are too small to compensate for the considerable dipolarity of the un-ionized barbituric acid ring; also it may be seen that barbital is appreciably ionized, which contributes to the relatively small permeability constant. Sulfaguanidine and acetylaminoantipyrine are both very polar molecules. Mecamylamine also might be considered an exception, since it shows a modest permeability even though strongly ionized; there is no dipolarity in mecamylamine except in the amino group.

Absorption of Drugs

Absorption is the process of movement of a drug from the site of application into the extracellular compartment of the body. Inasmuch as there is a great similarity among the various membranes that a drug may pass through in order to gain access to the extracellular fluid, it might be expected that the particular site of application (or route) would make little difference to the successful absorption of the drug. In actual fact, it makes a great deal of difference; many factors, other than the structure and composition of the membrane, determine the ease with which a drug is absorbed. These factors are discussed in the following sections, along with an account of the ways that drug formulations may be manipulated to alter the ability of a drug to be absorbed readily.

Routes of Administration

Drugs may be administered by many different routes. The various routes include oral, rectal, sublingual or buccal, parenteral, inhalation and topical. The choice of a route depends upon both convenience and necessity.

Oral Route—This is obviously the most convenient route for access to the systemic circulation, providing that various factors do not militate against this route. Oral administration does not always give rise to sufficiently high plasma concentrations to be effective; some drugs are absorbed unpredictably or erratically; patients occasionally have an absorption malfunction. Drugs may not be given by mouth to patients with gastrointestinal intolerance, or who are in preparation for anesthesia or who have had gastrointestinal surgery. Oral administration also is precluded in coma.

Rectal Route—Drugs that ordinarily are administered by the oral route usually can be administered by injection or by the alternative *lower enteric* route, through the anal portal

into the rectum or lower intestine. With regard to the latter, *rectal suppositories* or *retention enemas* formerly were used quite frequently, but their popularity has abated somewhat, owing to improvements in parenteral preparations. Nevertheless, they continue to be valid and, sometimes, very important ways of administering a drug, especially in pediatrics and geriatrics. In Fig 10⁸ the availability of a drug by retention enema may be compared with that by the intravenous and oral route and rectal suppository administration. It is apparent that the retention enema may be a very satisfactory means of administration but that rectal suppositories may be inadequate where rapid absorption and high plasma levels are required. The illustration is not intended to lead the reader to the conclusion that a retention enema always will give more prompt and higher blood levels than the oral route, for converse findings for the same drug have been reported,⁹ but, rather, to show that the retention enema may offer a useful substitute for the oral route.

Sublingual or Buccal Route—Even though an adequate plasma concentration eventually may be achievable by the oral route, it may rise much too slowly for use in some situations where a rapid response is desired. In such situations parenteral therapy usually is indicated. However, the patients with angina pectoris may get quite prompt relief from an acute attack by the *sublingual* or *buccal* administration of nitroglycerin, so that parenteral administration may be avoided. When only small amounts of drugs are required to gain access to the blood, the buccal route may be very satisfactory, providing the physicochemical prerequisites for absorption by this route are present in the drug and dosage form. Only a few drugs may be given successfully by this route.

Parenteral Routes—These routes, by definition, include any route other than the oral-gastrointestinal (enteric) tract,

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We gratefully acknowledge the co-operation of the surgical and gynaecological services of Stobhill General Hospital and Southern General Hospital, Glasgow.

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ritical bars represent a.d. \pm 30-40
mean 73 years, n = 8).

lowed the literature concerning the sensitivity of animal aortic evidence is conflicting. Carter (1977) found a decrease in sensitivity with age in the dog while (1978) found no change with age in these studies involved immature as opposed to a comparison of senescent. The present study of elderly subjects. There was no change in the sensitivity of human arterial aortic. This is found when the age is considered alone or when it is non-receptor mediated contractility.

ries for these experiments had to be with an underlying disease. to surgery, receiving medication adrenergic nervous system nor underlying arterial disease. Our ed by recent studies in vivo with eers (Elliot *et al.*, 1981) and with in young and old subjects).

can find no evidence *in vitro* that vascular α -adrenoceptor sensitivity increasing age. Further studies will examine whether changes in β -2 subtypes of α -adrenoceptors cardiovascular system).

BIOAVAILABILITY OF SUBLINGUAL ERGOTAMINE

Sublingual ergotamine has been used for years in the treatment of migraine attacks without any proof of its effectiveness. In a double-blind clinical trial no difference in relief was found between sublingual ergotamine and placebo (Crobbs *et al.*, 1964). Similarly, a study on the buccal absorption of ergotamine indicated that it is unlikely for therapeutically useful amounts of drug to be absorbed across the buccal membrane (Sutherland *et al.*, 1974).

In contrast, Winsor (1981) in a nonblind cross-over study with finger-plethysmography found that the peripheral vasoconstrictory effect of ergotamine was equal after 0.25 mg intramuscularly or 2 mg sublingually, and significantly different from sublingual placebo. The two forms at these doses should thus be equally effective in migraine. With a high performance liquid chromatographic (h.p.l.c.) assay for ergotamine, with a detection level of 0.1 ng/ml in plasma (Edlund, 1981), we have investigated several administration forms of the drug. The results for sublingual ergotamine are reported as they cast serious doubt on the equipotency of sublingual and intramuscular forms of ergotamine.

Four volunteers (medical personnel, non-

migraineurs) kept a sublingual tablet of 2 mg ergotamine tartrate (Lingraine[®], Wintthrop) under the tongue until dissolved. Blood was drawn after 5, 10, 20, 30, 60, 90 and 120 min. The samples were immediately centrifuged and kept deep frozen until analysed by the h.p.l.c. method. Ergotamine above the detection level was not found in any of the samples. Then the procedure was repeated in the same volunteers with another batch of Lingraine[®]. Again no ergotamine could be detected. The manufacturer informed us that both batches of Lingraine[®] were more than 2 years before their expiry date. For comparison we selected 4 migraine patients, who during the same period had their plasma levels of ergotamine determined with h.p.l.c. after 0.5 mg ergotamine tartrate/70 kg body weight intramuscularly. The mean and range of ergotamine levels in ng/ml plasma were after 30 min: 0.96 (0.48-1.41), after 60 min: 0.80 (0.57-1.07) and after 120 min: 0.57 (0.43-0.71). Even corrected to a dose of 0.25 mg the plasma levels of ergotamine are clearly above the detection level of 0.1 ng/ml.

These results were not obtained in a regular cross-over study. However, the discrepancy in plasma

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levels between sublingual and intramuscular ergotamine is so striking that it is unlikely for ergotamine 2 mg sublingually to have the same bioavailability as 0.25 mg intramuscularly.

Are the two forms of ergotamine then equipotent in their vasoconstrictory effect due to some active metabolites not measured by the specific h.p.l.c. method? Before going into speculations along these lines, we would suggest that the results with finger-plethysmography should be confirmed in a placebo-controlled double-blind study with direct measurements of the vasoconstrictory effect of ergotamine. Our main objection against the results with finger-plethysmography is that the effect of the reference form, intramuscular ergotamine, only had a duration of 90 min on venous occlusion blood flow. This short duration of action is not in agreement with recent investigations on arteries with ergotamine (Tfelt-Hansen *et al.*, 1980) and on veins with dihydroer-

gotamine (Aellig, 1981). The duration of these ergot alkaloids vasoconstrictory effect in man was found to be at least 24 and 8 h respectively. Further, a dose-response curve for the biological effect should be established before the question of biological equipotency can be answered satisfactorily.

If proven to be equipotent to parenteral ergotamine in such studies, sublingual ergotamine should undergo a controlled clinical trial in migraine.

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VERAPAMIL BIOAVAILABILITY AND DOSAGE IN LIVER DISEASE

May we be permitted to comment on the critical remarks made by Somogyi *et al.* (1981) on our dosage recommendations for verapamil and at the same time discuss the wider significance of verapamil dosage in liver disease.

Somogyi *et al.* (1981) recommend that the oral dose of verapamil in liver cirrhosis patients should be greatly reduced, and more so than required in the case of the intravenous dose. The oral dose they recommend is as little as one fifth of that used in patients with normal liver function. In our dosage recommendations, based on intravenous administration in patients with cirrhosis, hepatitis and fatty liver disease, a reduction to about one third was indicated, although there was considerable inter-patient variation (Woodcock *et al.*, 1979). Verapamil clearance data following oral treatment in liver patients were not available at this time. Somogyi *et al.* (1981) state that we 'failed to appreciate the difference between oral and intravenous clearance of verapamil' and thus imply that we were erroneous in the interpretation of

our observations. This statement, apart from being incorrect (the first pass effect of verapamil is common knowledge since the report of Shomenus *et al.* (1976), misses the fundamental point which is that the large reduction, to one fifth, in the oral dose of verapamil recommended by themselves, applies only to liver cirrhosis patients who have marked intra- and extra-hepatic shunts. This fact was omitted from their discussion.

We have reported observations on liver cirrhosis patients in whom the bioavailability of verapamil was the same as in healthy subjects despite a greatly reduced systemic clearance (Woodcock *et al.*, 1981). In patients with fatty liver the first pass extraction was increased and the bioavailability actually lower than normal. A higher than normal extraction of verapamil is, according to Wilkinson & Shand (1975), to be expected when the rate of blood flow through the liver is reduced. In these patients there was thus no evidence for the development of hepatic shunts and dosage reduction of the magnitude suggested by

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Somogyi *et al.* (1981) patients studied by Sor and were undergoin because of excessive c therefore a selected g verapamil bioavailabi normal and thus the c is a pathological char to use the verapan patients to make goe all liver patients is cle

Liver disease pati verapamil clearance increased, unchanged suitable dosage reg necessary to consider patient. Our present dose to achieve an however, and a th plasma concentration We now know, th that the intrinsicle bility in liver dis (Woodcock *et al.*, 19

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Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS. 10/e

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tone is low (Marshall *et al.*, 1987; Hanel and Lands, 1982). Further, acetaminophen does not inhibit neutrophil activation as do other NSAIDs (Abramson and Weissmann, 1989).

Single or repeated therapeutic doses of acetaminophen have no effect on the cardiovascular and respiratory systems. Acid-base changes do not occur, nor does the drug produce the gastric irritation, erosion, or bleeding that may occur after administration of salicylates. Acetaminophen has no effects on platelets, bleeding time, or the excretion of uric acid.

Pharmacokinetics and Metabolism. Acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract. The concentration in plasma reaches a peak in 30 to 60 minutes, and the half-life in plasma is about 2 hours after therapeutic doses. Acetaminophen is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma proteins is variable; only 20% to 50% may be bound at the concentrations encountered during acute intoxication. After therapeutic doses, 90% to 100% of the drug may be recovered in the urine within the first day, primarily after hepatic conjugation with glucuronic acid (about 60%), sulfuric acid (about 35%), or cysteine (about 3%); small amounts of hydroxylated and deacetylated metabolites also have been detected. Children have less capacity for glucuronidation of the drug than do adults. A small proportion of acetaminophen undergoes cytochrome P450-mediated *N*-hydroxylation to form *N*-acetyl-benzoquinonimine, a highly reactive intermediate. This metabolite normally reacts with sulfhydryl groups in glutathione. However, after ingestion of large doses of acetaminophen, the metabolite is formed in amounts sufficient to deplete hepatic glutathione (see below).

Therapeutic Uses. Acetaminophen is a suitable substitute for aspirin for analgesic or antipyretic uses; it is particularly valuable for patients in whom aspirin is contraindicated (e.g., those with peptic ulcer) or when the prolongation of bleeding time caused by aspirin would be a disadvantage. The conventional oral dose of acetaminophen is 325 to 1000 mg (650 mg rectally); the total daily dose should not exceed 4000 mg. For children, the single dose is 40 to 480 mg, depending upon age and weight; no more than five doses should be administered in 24 hours. A dose of 10 mg/kg also may be used.

Toxic Effects. In recommended therapeutic dosage, acetaminophen usually is well tolerated. Skin rash and other allergic reactions occur occasionally. The rash is usually erythematous or urticarial, but sometimes it is more serious and may be accompanied by drug fever and mucosal lesions. Patients who show hypersensitivity reactions to the salicylates only rarely exhibit sensitivity to acetaminophen. In a few isolated cases, the use of acetaminophen has been associated with neutropenia, thrombocytopenia, and pancytopenia.

The most serious adverse effect of acute overdosage of acetaminophen is a dose-dependent, potentially fatal hepatic necrosis (see Thomas, 1993). Renal tubular necrosis and hypoglycemic coma also may occur. The mechanism by which overdosage with acetaminophen leads to hepatocellular injury and death involves its conversion to a toxic reactive metabolite (see also Chapter 4). Minor pathways of acetaminophen elimination are via conjugation with glucuronide and sulfate. The major pathway of metabolism is via cytochrome P450s to the intermediate, *N*-acetyl-*para*-benzoquinonimine, which is very elec-

trophilic. Under normal circumstances, this intermediate is inactivated by conjugation with glutathione (GSH) and then metabolized to a mercapturic acid and excreted into the urine. However, in the setting of acetaminophen overdose, hepatic levels of GSH become depleted. Two consequences result of depletion of GSH. Since GSH is an important component in antioxidant defense, hepatocytes are rendered highly susceptible to oxidant injury. Depletion of GSH also allows the intermediate to bind covalently to cell macromolecules, leading to dysfunction of enzymatic systems.

Hepatotoxicity. In adults, hepatotoxicity may occur after ingestion of a single dose of 10 to 15 g (150 to 250 mg/kg) of acetaminophen; doses of 20 to 25 g or more are potentially fatal. Alcoholics can have hepatotoxicity with much lower doses, even with doses in the therapeutic range. The mechanism of this effect is discussed above (see also Chapter 4). Symptoms that occur during the first 2 days of acute poisoning by acetaminophen may not reflect the potential seriousness of the intoxication. Nausea, vomiting, anorexia, diaphoresis, and abdominal pain occur during the initial 24 hours and may persist for a week or more. Clinical indications of hepatic damage become manifest within 2 to 4 days of ingestion of toxic doses; aspartate aminotransferases are elevated (sometimes markedly), and the concentration of bilirubin in plasma may be increased. In addition, the prothrombin time is prolonged. Perhaps 10% to 20% of poisoned patients who do not receive specific treatment develop severe liver damage; of these, 10% to 20% eventually die of hepatic failure. Acute renal failure also occurs in some patients. Biopsy of the liver reveals centrilobular necrosis with involvement of the periportal area. In nonfatal cases, the hepatic lesion is reversible over a period of weeks or months.

Severe liver damage (with levels of aspartate aminotransferase activity in excess of 1000 IU per liter of plasma) occurs in 90% of patients with plasma concentrations of acetaminophen greater than 300 µg/ml at 4 hours or 45 µg/ml at 15 hours after the ingestion of the drug. Minimal hepatic damage is anticipated when the drug concentration is less than 120 µg/ml at 4 hours or 30 µg/ml at 12 hours after ingestion. The potential severity of hepatic necrosis also can be predicted from the half-life of acetaminophen observed in the patient; greater than 4 hours imply that necrosis will occur, while greater than 12 hours suggest that hepatic coma is likely. The nomogram provided in Figure 27-2 relates the plasma level of acetaminophen and time after ingestion to the predicted extent of liver injury (see Rumack *et al.*, 1981).

Early diagnosis is vital in the treatment of overdosage of acetaminophen, and methods are available for the rapid determination of concentrations of the drug in plasma. However, treatment should not be delayed while awaiting laboratory results. If the clinical history suggests a significant overdosage, vigorous supportive therapy is essential when intoxication is severe. Gastric lavage should be performed in all cases, preferably within 4 hours of the ingestion.

The principal antidotal treatment is the administration of sulfhydryl compounds, which probably act, in part, by replenishing hepatic stores of glutathione. *N*-acetylcysteine (MUCOSIL) is effective when given orally or intravenously. The intravenous form is available in Europe, where it is considered the treatment of choice. When given orally, the *N*-acetylcysteine solution (which has a foul smell and taste) is diluted with

Table A-II-1
PHARMACOKINETIC DATA

AVAILABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE (ml · min ⁻¹ · kg ⁻¹)	VOL. DIST. (liters/kg)	HALF-LIFE (hours)	PEAK TIME (hours)	PEAK CONCENTRATIONS
ABACAVIR (Chapter 51)							
83 (63-110)	1 (0-4)	—	12.8 (9.3-17.5)	0.84 (0.69-1.03)	1.0 (0.8-1.3)	Tab: 0.63 (0.4-1.1) ^b Sol: 0.5 (0.5-0.6) ^b	Tab: 2.6 (2.3-2.9) μg/ml ^b Sol: 2.9 (2.5-3.4) μg/ml ^b

^aData from male subjects with HIV infection. Values are geometric means and 95% CI. Metabolized by ADH, UGT, and other enzymes.

^bC_{max} and T_{max} (geometric mean and 95% CI) following a 300-mg oral tablet (Tab) or solution (Sol).

Reference: Barry, M., Mulcahy, E., Merry, C., Gibbons, S., and Back, D. Pharmacokinetics and potential interactions amongst antiretroviral agents used to treat patients with HIV infection. *Clin. Pharmacokinet.* 1999, 36:289-304.

Childs, G.E., Gillotin, C., McDowell, J.A., Low, Y., Edwards, K.D., Prince, W.T., and Stein, D.S. Abacavir: absolute bioavailability, bioequivalence of three oral formulations, and effect of food. *Pharmacotherapy*, 1999, 19:932-942.

ACETAMINOPHEN (Chapter 27)

88 ± 15 ↔ Child	3 ± 1 ↔ Neo, Child	<20	5.0 ± 1.4 ^b ↓ Hep ^c ↔ Aged, Child ↑ Obes, HTN, Preg	0.95 ± 0.12 ^b ↔ Aged, Hep ^c LTH, HTN, Child	2.0 ± 0.4 ↔ RD, Obes, Child ↑ Neo, Hep ^c ↓ HTN, Preg	0.33-1.4 ^d	20 μg/ml ^e
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^aValues reported are for a linear three-compartment model for doses less than 2 g; drug exhibits concentration-dependent kinetics above this dose.

^bAssuming a 70-kg body weight; reported range, 65 to 72 kg.

^cAcetaminophen-induced hepatic damage or acute viral hepatitis.

^dAbsorption rate, but not extent, depends on gastric emptying; hence, allowed after food as well as in some disease states and concomitant with drugs that cause gastroparesis.

^eMean concentration following a 20-mg/kg oral dose. Hepatic toxicity associated with levels >300 μg/ml at 4 hours after an overdose.

1924

(S)-5-(1-ACETYL-4-METHADOL-1-AMINO) (Chapter 23)

47 ± 5	6	80	4.93 ± 0.58	7.0	L: 18.5 ± 4.9 NL: 23.9 ± 3.2 DL: 63.8 ± 10.1	L: 2.6 ± 0.2 ^b NL: 3.9 ± 0.7 ^b DL: 31 ± 9.6 ^b	L: 63 ± 8 ng/ml ^b NL: 44 ± 4 ng/ml ^b DL: 19 ± 1 ng/ml ^b
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^aData from healthy adult male subjects. LAAM (L) is metabolized by cytochrome P450 (primarily CYP2A) to active metabolites, mono-LAAM (NL) and di-LAAM (DL).

^bFollowing a single 40-mg oral dose.

Reference: Kulka, R.P., Chantelle, N., and Jurek, C.E. Simultaneous determination of acetaminophen and its active biotransformation products in human biofluids. *J. Chromatogr.* 1974, 109:247-258.

Wahle, S.L., Johnson, R.E., Dene, E.J., and Bigelow, G.E. Intravenous and oral *(S)*-5-(1-acetyl-4-methadol-1-amino) pharmacokinetics and pharmacokinetics in humans. *J. Pharmacol. Exp. Ther.* 1998, 285:71-81.

ACETYL-SALICYLIC ACID (Chapter 27, 55)

68 ± 3 ↔ Aged, Cir	1.4 ± 1.2	49 ↓ RD	9.3 ± 1.1 ↔ Aged, Cir	0.15 ± 0.03	0.25 ± 0.03 ↔ Hep	0.39 ± 0.21 ^b	24 ± 4 μg/ml ^b
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^aValues given are for unchanged parent drug. Acetylsalicylic acid is converted to salicylic acid during and after absorption (C₂ and C₃ of salicylates are dose-dependent; half-life varies between 2-4 hours after a 300-mg dose to 15 hours when there is intoxication).

^bValues given are for unchanged parent drug. Acetylsalicylic acid is converted to salicylic acid during and after absorption (C₂ and C₃ of salicylates are dose-dependent; half-life varies between 2-4 hours after a 300-mg dose to 15 hours when there is intoxication).

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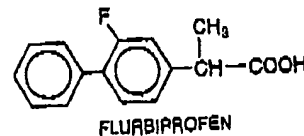
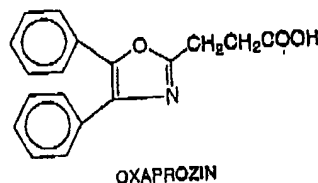
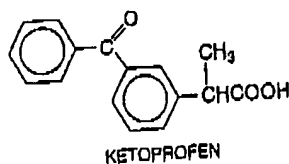
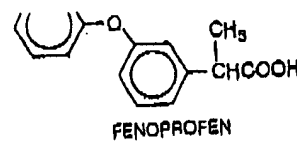
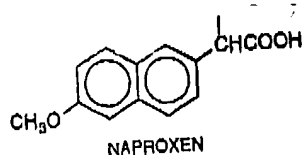
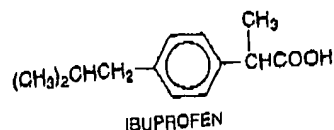


Figure 27-3. Structural formulas of antiinflammatory propionic acid derivatives.

With this drug is greater. It is available for sale without a prescription in the United States. Naproxen has a longer half-life than most of the other structurally and functionally similar agents, making twice-daily administration of it feasible. This drug also is available without a prescription in the United States. Oxaprozin also has a long half-life and can be given once daily. The structural formulas of these drugs are shown in Figure 27-3.

Pharmacological Properties. The pharmacodynamic properties of the propionic acid derivatives do not differ significantly. All are effective cyclooxygenase inhibitors, although there is considerable variation in their potency. For example, naproxen is approximately 20 times more potent than aspirin, while ibuprofen, fenoprofen, and aspirin are roughly equipotent as cyclooxygenase inhibitors. All of these agents alter platelet function and prolong bleeding time, and it should be assumed that any patient who is intolerant of aspirin also will experience a severe reaction after administration of one of these drugs. Some of the propionic acid derivatives have prominent inhibitory effects on leukocyte function; naproxen is particularly potent in this regard. While the compounds do vary in potency, this is not of obvious clinical significance. All are effective antiinflammatory agents in various experimental animal models of inflammation; all have useful antiinflammatory, analgesic, and antipyretic activities in human beings. Although all of these compounds can cause gastric toxicity in patients, these are usually less severe than with aspirin.

It is difficult to find data on which to base a rational choice among the members of the propionic acid derivatives, if in fact one can be made. However, in relatively small clinical studies that compared the activity of several members of this group, patients preferred naproxen in terms of analgesia and relief of morning stiffness (see

Huskisson, in Symposium, 1983a; Hart and Huskisson, 1984). With regard to side effects, naproxen was the best tolerated, followed by ibuprofen and fenoprofen. There was considerable interpatient variation in the preference for a single drug and also between the designations of the best and the worst drug. Unfortunately, it is probably impossible to predict *a priori* which drug will be most suitable for any given individual. Nevertheless, more than 50% of patients with rheumatoid arthritis probably will achieve adequate symptomatic relief from the use of one or another of the propionic acid derivatives, and many clinicians favor their use instead of aspirin in such patients.

Drug Interactions. The potential adverse drug interactions of particular concern with propionic acid derivatives result from their high degree of binding to albumin in plasma. However, the propionic acid derivatives do not alter the effects of the oral hypoglycemic drugs or warfarin. Nevertheless, the physician should be prepared to adjust the dosage of warfarin because these drugs impair platelet function and may cause gastrointestinal lesions.

Ibuprofen

Ibuprofen is supplied as tablets containing 200 to 800 mg; of the 200-mg tablets (ADVIL, NUPRIN, others) are available with a prescription.

For rheumatoid arthritis and osteoarthritis, daily doses up to 3200 mg in divided portions may be given, although usual total dose is 1200 to 1800 mg. It also may be possible to reduce the dosage for maintenance purposes. For mild to moderate pain, especially that of primary dysmenorrhea, the usual dosage is 400 mg every 4 to 6 hours as needed. The drug may be given with milk or food to minimize gastrointestinal side effects. *Ibuprofen* has been discussed in detail by Kaizer (1979) and by Adams and Buckler (in Symposium, 1983a).

Pharmacokinetics and Metabolism. *Ibuprofen* is rapidly absorbed after oral administration, and peak concentration

Table A-II-1
PHARMACOKINETIC DATA (Continued)

AVAILABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE (ml·min ⁻¹ ·kg ⁻¹)	VOL. DIST. (liters/kg)	HALF-LIFE (hours)	PEAK TIME (hours)	PEAK CONCENTRATIONS
HYDROMORPHONE^a (Chapter 23)							
Oral: 42 ± 23 SC: ~80	6	7.1	14.6 ± 7.6	2.90 ± 1.31 ^b	2.4 ± 0.6	IV: ~ ^c Oral: 1.1 ± 0.2 ^c	IV: 242 ng/ml ^c Oral: 11.8 ± 2.6 ng/ml ^c
^a Data from healthy male subjects. Extensively metabolized. The principal metabolite, 3-glucuronide, accumulates to much higher (21-404) levels than parent drug, and may contribute to some side effects (not antitoxicopne). ^b Values reported. ^c Following a single 2-mg IV (bolus, sample at 3 minutes) or 4-mg oral dose.							
HYDROXYUREA^a (Chapter 52)							
108 ± 18 79-108	35.8 ± 14.2	Negligible	72 ± 17 ml·min ⁻¹ (m ²) ^{-1b} (36.2-72.3)	19.7 ± 4.6 l/m ²	3.4 ± 0.7 (2.8-4.5)	IV: 0.5 ^c Oral: 1.2 ± 1.2 ^c	IV: 1007 ± 371 μM ^c Oral: 794 ± 241 μM ^c
^a Data from male and female patients treated for solid tumors. A range of mean values from multiple studies is shown in parentheses. ^b Normal elimination of hydroxyurea is thought to exhibit saturable kinetics through a 10- to 100-mg dose range. ^c Following a single 2-g, 30-minute intravenous infusion or oral dose.							
IBUPROFEN^a (Chapter 27)							
~80	<1	>99 ^b ↔ RA, Alb	0.75 ± 0.20 ^{b,c} ↑ CF ↔ Child, RA	0.15 ± 0.02 ^c ↑ CF	1.2 ± 0.5 ^b ↔ RA, CF, Child ↑ Ctr	1.6 ± 0.3 ^d	61.1 ± 5.5 μg/ml ^d
^a Racemic mixture. Kinetic parameters for the active S-(+)-enantiomer do not differ from those for the inactive R-(-)-enantiomer when administered separately; 63 ± 6% of the R-(-)-enantiomer undergoes inversion to the active form. ^b Unbound percent of S-(+)-ibuprofen (0.77 ± 0.20%) is significantly greater than that of R-(-)-ibuprofen (0.45 ± 0.06%). Binding of each enantiomer is concentration dependent and is influenced by the presence of the optical isotope, leading to nonlinear elimination kinetics. ^c CLF and V _d /F reported. ^d Following a single 800-mg dose of racemate. A level of 10 μg/ml provides antipyresis in febrile children.							

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